REMARKS

Applicants respectfully request reconsideration and allowance in view of this Supplemental Amendment.

Applicants present their claims 94-121, 123, 124, 129-136 and 137-142 for examination. Amended claims are presented solely for clarification but without narrowing claim scope. The new claims find basis in the original application and the claims previously presented for examination.

Applicants respectfully submit their application has already been previously scrutinized by Examiners, such as Examiners Budens and Brown, who have issued Office Actions. *See, e.g.*, Office Actions in 2001, 2002 and 2004, among others. Such Examiners considered the claims.

It is not seen that a requirement for restriction is either appropriate after other prior Examiners reviewed all the claims. Indeed, it is certainly not fair to impose a restriction requirement on a small entity well into patent prosecution, and well after other Office Actions on the merits, including a now withdrawn Final Rejection, and certainly it is inequitable to restrict claims after an Office Action on the merits for claims now under consideration.

Applicants have earlier suffered through the unavailability of their original, initial foreign patent agent (health reasons). Applicants have since tried to maintain their application alive while trying to obtain funding to move the technology towards commercial fruition. Under the circumstances, a restriction at this point in time years into prosecution is an unfortunate, unwanted financial burden on Applicants. It is respectfully submitted that the cost for separate

prosecution and exposure to maintenance fees for multiple cases is, to put it delicately, a *de facto* tax.

Applicants have also considered the Katre document but find its citation odd in the context of an untimely requirement for restriction. In Applicants' view, the Katre reference does not furnish 'substantial evidence' to support the restriction requirement. *Arguendo*, Katre at page 1, lines 3-5 refers to succinylation of IL-2 to render it soluble at physiological pH, but the methodology disclosed undermines the apparent thesis to the restriction requirement. For instance, at page 13, lines 27-28 Katre did not determine solubility of di-succinyl IL-2, and at page 8, lines 16-18 it's mentioned that cold storage at 4 °C for 3 days or physical agitation at RT causes visible precipitation of IL-2 protein, and does not appear to disclose or suggest gradually varying conditions (Applicants' claim 104, for example), inasmuch as Katre reports such ide variance in specific bioactivity (page 13, lines 15-18) as to call into question - in Applicants' present opinion, whether there was or was not even a measurable systematic difference between the materials being compared in Katre (page 13, lines 7-9). Put another way, inasmuch as the cited art apparently implies, if it does not suggest, deterioration of results by 30% of original activity, Applicants suggest the reference neither teaches the present inventions nor supports the restriction requirements, especially since it implies a modified substance clears faster from blood in testing. The Katre reference appears in Applicants' present opinion to be consistent with problems associated with the "SDS", which molecules are sometimes hard to remove thereby causing quantitative interpretations unreliable, as seen from the statement at page 12, lines 17-18 about trying to remove SDS. Accordingly, Applicants' present view is that a person skilled in the art would not have considered Katre as either a springboard to the present claimed

inventions, or as a basis to slice this application into five (5) Groups years after other examiners have been able to examine the case and issued office actions on the merits.

Applicants furthermore courteously submit that even if an untimely restriction requirement were to be maintained, despite the prior scrutiny of the claims, that the Groups proposed should be reconsidered, re-formed, and consolidated for examination.

Even if all Groups are not combined, which then at least, for instance, the claims in Group I, Group IV and Group V are related and these claims should be combined for examination on the merits. Group I claim 107 refers to a zinc binding center. Group V is a subset of Group IV. Groups IV and V are exemplifications of what a person skilled in the art could obtain - following the teachings in the present specification - by practicing the Group I claimed inventions. Thus, as a minimum, these Groups of claims should be considered together.

Applicants therefore further submit, *arguendo*, that at least Groups I, IV and V should be re-formed, and re-joined as one group. The Examiner will appreciate that claims 94-111, 133, and 136 are related through claim dependency to new claims 137-142 (as a contingently elected group of claims, subject to this and all prior traverses). As a consequence, Group I includes such new claims 137-142, and thus at a minimum Group I should thus be reformed to be a combination of Groups I, IV and V.

Accordingly, a methodology with electrospray mass spectroscopy (Group I), a protein hormone (Group IV) and a zinc binding signal substance, *e.g.,* zinc binding signal peptides (Group V), are proposed as an alternative contingent 'election,' on the basis of the reformed grouping of claims, assuming the restriction is not withdrawn in its entirety as it should be. (Contingently, and subject to traverse and to the request to reform the restriction requirement,

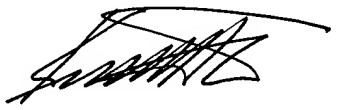
electrospray mass spectroscopy, signal peptides and signal proteins, and zinc binding signal peptides are elected species.) .

Furthermore, when the claims are re-grouped at least claims 94-111, 112, 113, 114, 115, 116-117, 118-120, 121, 123, 131, 133, 134 and 135, 136 and 137-142 should be considered together and as such are further alternatively contingently elected, subject to all traverses previously of record, and without prejudice to Applicants petitioning for relief against the untimely restriction requirement.

Applicants courteously solicit reconsideration and withdrawal of the untimely requirement for restriction, and in the alternative courteously solicit reformation of the requirement for restriction to combine the claims in at least Groups I, IV and V, with the provisional, contingent elections as noted herein.

An interview with the Examiner is respectfully solicited.

Respectfully submitted,



Date: **December 15, 2006**

Kendrew H. Colton
Registration No. 30,368

OFFICIAL CORRESPONDENCE TO
Customer No. 42798

FITCH, EVEN, TABIN & FLANNERY
One Lafayette Centre
1120 20th Street, NW, Suite 750 South
Washington, DC 20036
Tel: (202) 419-7000
Fax: (202) 419-7007